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EXAMINER

BERTAGNA, ANGELA MARIE

ART UNIT

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1637

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/813,693	<b>Applicant(s)</b> TABOR ET AL.	
	<b>Examiner</b> ANGELA BERTAGNA	<b>Art Unit</b> 1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 02 March 2009.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 1, 11, 24, 124-159, 161-166, 168 and 169 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1, 11, 24, 124-159, 161-166, 168 and 169 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                     | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____                                      |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)          | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____  | 6) <input type="checkbox"/> Other: _____                          |

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## **DETAILED ACTION**

### ***Status of the Application***

1. Applicant's response filed on March 2, 2009 is acknowledged. Claims 1, 11, 24, 124-159, 161-166, 168, and 169 are currently pending.

Applicant's arguments and the declaration under 37 CFR 1.132 filed on March 2, 2009 have been fully considered, but they were not persuasive for the reasons set forth below. Accordingly, this Office Action is made **FINAL**.

### ***Claim Rejections - 35 USC § 103***

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

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3. Claims 1, 11, 129-139, 141-147, 156, and 165 are rejected under 35 U.S.C. 103(a) as being unpatentable over Scherzinger et al. (European Journal of Biochemistry (1977) 72: 543-558; cited previously) in view of Sorge et al. (US 5,556,772; cited previously) and further in view of Tabor et al. (The Journal of Biological Chemistry (1989) 264(11): 6447-6458; cited previously).

These claims are drawn to a method for isothermally amplifying DNA in the absence of exogenous primers.

Scherzinger teaches a method for isothermal DNA amplification in the absence of exogenous nucleic acid primers (page 546, column 1).

Regarding claims 1, 11, 130, 131, 137-139, 141, 156, and 165, the method of Scherzinger comprises amplifying a template DNA molecule under isothermal conditions in a reaction mixture that comprises the DNA template, T7 DNA polymerase, a helicase from bacteriophage T7, a primase from bacteriophage T7, and a single-stranded DNA binding protein (see page 546, column 1). The amplification method of Scherzinger does not require the addition of exogenously added primers, and the template DNA molecule does not have a terminal protein covalently attached to either 5' end. Scherzinger teaches that the amount of amplified product produced by the method is as much as 4-fold greater than the amount of template put into the reaction mixture (page 549, column 2).

Regarding claim 142, Scherzinger teaches that the above method can be performed using an *E. coli* single-stranded DNA binding protein (page 549, column 2).

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Regarding claims 143-147, Scherzinger teaches that the amplification is conducted at 30°C, which is less than 60°C, less than 50°C, less than 45°C, less than 40°C, and about 37°C (page 546, column 1).

Scherzinger does not teach that the yield of amplified product is at least 10-fold greater than the amount of template DNA present at the start of the reaction.

Sorge teaches a composition which comprises a DNA polymerase with substantial 3'-5' exonuclease activity and DNA polymerase modified to have reduced 3' to 5' exonuclease activity (column 2, lines 63-66). Sorge further teaches that wild-type T7 DNA possesses substantial 3' to 5' exonuclease activity (column 3, lines 44-47), whereas modified T7 DNA polymerase has reduced 3' to 5' exonuclease activity (column 4, lines 5-10). Regarding claims 1, 11, 129, 132, and 165, Sorge teaches that conducting amplification reactions in the presence of a DNA polymerase that possesses substantial 3' to 5' exonuclease activity and a DNA polymerase substantially lacking in 3' to 5' exonuclease activity, "increases synthesis product yield, increased transcription product length, and the synthesis of polynucleotides that can not be synthesized by a given polymerase alone (column 3, lines 22-27)."

Regarding claims 135 and 136, Sorge teaches that the ratio of the two polymerases should be optimized by routine experimentation (column 4, lines 45-58) and further teaches compositions wherein the ratio of the polymerase lacking 3' to 5' exonuclease activity to the polymerase possessing 3' to 5' exonuclease activity is 10:1 (see Table in column 14).

Tabor teaches wild-type and variant forms of T7 DNA polymerase (see abstract). Regarding claims 133 and 134, Tabor teaches that the wild-type T7 DNA polymerase has about

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5,000 units of exonuclease activity per milligram of protein, whereas the variant form has less than 50% of the wild-type exonuclease activity (see Table IV on page 6455).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of invention to further include a T7 DNA polymerase substantially lacking in 3' to 5' exonuclease activity in the reaction mixture taught by Scherzinger. An ordinary artisan would have been motivated to do so in order to provide an improved system for *in vitro* DNA synthesis, since Sorge stated that amplification in the presence of a DNA polymerase that possesses substantial 3' to 5' exonuclease activity and a DNA polymerase substantially lacking in 3' to 5' exonuclease activity, "increases synthesis product yield, increased transcription product length, and the synthesis of polynucleotides that can not be synthesized by a given polymerase alone (column 3, lines 22-27)." Finally, an ordinary artisan also would have been motivated to optimize the ratio of the two polymerases to maximize the reaction yield (*e.g.* to generate at least 10-fold amplification) with a reasonable expectation of success, since Sorge expressly taught that the concentrations of the two polymerases should be optimized by routine experimentation (column 4, lines 45-58). Moreover, as noted *In re Aller*, 105 USPQ 233 at 235, "More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." Routine optimization is not considered inventive and no evidence has been presented that the selection of the claimed polymerase ratios was other than routine or that the results should be considered unexpected in any way as compared to the closest prior art.

Finally, regarding the claimed amplification yield of at least 10-fold, attention is also directed to *KSR Int'l Co. v. Teleflex Inc.* (550 U.S. \_\_\_\_, 127 S. Ct. 1727 (2007)) where the

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Supreme Court determined that “a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103 (*KSR*, 550 U.S. at \_\_\_\_, 82 USPQ2d at 1397).”

In this case, as discussed above, Scherzinger taught an isothermal, primer-independent DNA amplification method that resulted in up to 4-fold amplification of the target nucleic acid. Since Sorge taught that the use of a T7 DNA polymerase possessing 3' to 5' exonuclease activity in combination with a T7 DNA polymerase substantially lacking 3' to 5' exonuclease activity, such as the modified T7 DNA polymerase taught by Tabor, improved the yield of DNA synthesis reactions (column 3, lines 22-27), an ordinary artisan would have been motivated to use such a combination of polymerases in the method of Scherzinger to improve the yield of the DNA synthesis reaction. An ordinary artisan also would have been motivated to optimize results-effective variables such as polymerase concentrations, salt concentrations, pH, and temperature by routine experimentation in order to maximize the reaction yield. These methods of improving the yield of *in vitro* DNA amplification reactions were within the technical grasp of the ordinary artisan, and their application to the method resulting from the combined teachings of Scherzinger and Sorge would lead to the anticipated success. Thus, the methods of claims 1, 11, 129-139, 141-147, 156, and 165 are *prima facie* obvious in view of the combined teachings of Scherzinger, Sorge, and Tabor in the absence of secondary considerations.

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4. Claim 24 is rejected under 35 U.S.C. 103(a) as being unpatentable over Scherzinger et al. (European Journal of Biochemistry (1977) 72: 543-558; cited previously) in view of Sorge et al. (US 5,556,772; cited previously) and further in view of Bernstein et al. (Proceedings of the National Academy of Sciences, USA (1988) 85: 396-400; cited previously).

Regarding claim 24, Scherzinger teaches a method for amplifying a DNA molecule comprising amplifying a template DNA molecule under isothermal conditions in a reaction mixture that comprises the DNA template, wild-type T7 DNA polymerase, a helicase from bacteriophage T7, a primase from bacteriophage T7, and a single-stranded DNA binding protein (see page 546, column 1). The amplification method of Scherzinger does not require the addition of exogenously added primers, and the template DNA molecule does not have a terminal protein covalently attached to either 5' end. Scherzinger teaches that the amount of amplified product produced by the method is as much as 4-fold greater than the amount of template put into the reaction mixture (page 549, column 2).

Scherzinger does not teach that the reaction further comprises a variant T7 DNA polymerase modified to possess reduced 3' to 5' exonuclease activity as required by claim 24. Also, Scherzinger teaches using the 66-kDa or 58-kDa form of the T7 gene 4 protein rather than the 63-kDa form required by claim 24. Finally, Scherzinger does not teach that the yield of amplified product is at least 10-fold greater than the amount of template DNA present at the start of the reaction.

Sorge teaches a composition which comprises a DNA polymerase with substantial 3'-5' exonuclease activity and a DNA polymerase modified to have reduced 3' to 5' exonuclease activity (column 2, lines 63-66). Sorge further teaches that wild-type T7 DNA polymerase



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possesses substantial 3' to 5' exonuclease activity (column 3, lines 44-47), whereas modified T7 DNA polymerase has reduced 3' to 5' exonuclease activity (column 4, lines 5-10). Regarding claim 24, Sorge teaches that conducting amplification reactions in the presence of a DNA polymerase that possesses substantial 3' to 5' exonuclease activity and a DNA polymerase substantially lacking in 3' to 5' exonuclease activity, "increases synthesis product yield, increased transcription product length, and the synthesis of polynucleotides that can not be synthesized by a given polymerase alone (column 3, lines 22-27)."

Bernstein compared the 56 kDa and 63 kDa forms of the T7 gene 4 protein (see abstract). Regarding claim 24, Bernstein teaches that the 7 kDa region absent from the 56 kDa form of the gene 4 protein is required for primase activity (see abstract and page 398).

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to apply the teachings of Sorge and Bernstein to the method taught by Scherzinger. An ordinary artisan would have been motivated to further include a T7 DNA polymerase substantially lacking in 3' to 5' exonuclease activity in the reaction mixture taught by Scherzinger, since Sorge stated that amplification in the presence of a DNA polymerase that possesses substantial 3' to 5' exonuclease activity and a DNA polymerase substantially lacking in 3' to 5' exonuclease activity, "increases synthesis product yield, increased transcription product length, and the synthesis of polynucleotides that can not be synthesized by a given polymerase alone (column 3, lines 22-27)." An ordinary artisan also would have been motivated to utilize the 63-kDa form of the T7 gene 4 protein in the method taught by Scherzinger, since Bernstein taught that this protein contained the 7 kDa region critical for primase activity (see abstract and page 398). Finally, an ordinary artisan also would have been motivated to optimize the ratio of

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the two DNA polymerases in order to maximize the reaction yield (*e.g.* to generate at least 10-fold amplification) with a reasonable expectation of success, since Sorge expressly taught that the concentrations of the two polymerases should be optimized by routine experimentation (column 4, lines 45-58). As noted in *In re Aller*, 105 USPQ 233 at 235, “Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.” Routine optimization is not considered inventive and no evidence has been presented that the selection of the claimed polymerase ratios was other than routine or that the results should be considered unexpected in any way as compared to the closest prior art.

Finally, regarding the claimed amplification yield of at least 10-fold, attention is also directed to *KSR Int’l Co. v. Teleflex Inc.* (550 U.S. \_\_\_\_, 127 S. Ct. 1727 (2007)) where the Supreme Court determined that “a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103 (*KSR*, 550 U.S. at \_\_\_\_, 82 USPQ2d at 1397).”

In this case, as discussed above, Scherzinger taught an isothermal, primer-independent DNA amplification method that resulted in 4-fold amplification of the target nucleic acid. Since Sorge taught that the use of a T7 DNA polymerase possessing 3' to 5' exonuclease activity in combination with a T7 DNA polymerase substantially lacking 3' to 5' exonuclease activity improved the yield of DNA synthesis reactions (column 3, lines 22-27), an ordinary artisan would have been motivated to use such a combination of polymerases in the method of

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Scherzinger to improve the yield of the DNA synthesis reaction. An ordinary artisan would have been motivated to optimize results-effective variables such as polymerase concentrations, salt concentrations, pH, and temperature by routine experimentation in order to maximize the reaction yield. These methods of improving the yield of in vitro DNA amplification reactions were within the technical grasp of the ordinary artisan, and their application to the method resulting from the combined teachings of Scherzinger and Sorge would lead to the anticipated success. Thus, the method of claim 24 is *prima facie* obvious in view of the combined teachings of Scherzinger, Sorge, and Bernstein in the absence of secondary considerations.

5. Claims 124-128, 157-159, 166, and 168 are rejected under 35 U.S.C. 103(a) as being unpatentable over Scherzinger et al. (European Journal of Biochemistry (1977) 72: 543-558; cited previously) in view of Sorge et al. (US 5,556,772; cited previously) and further in view of Tabor et al. (The Journal of Biological Chemistry (1989) 264(11): 6447-6458; cited previously) and further in view of Walker et al. (Nucleic Acids Research (1992) 20(7): 1691-1696; cited previously).

The combined teachings of Scherzinger, Sorge, and Tabor result in the method of claims 1, 11, 129-139, 141-147, 156, and 165, as discussed above.

Regarding claims 166 and 168, Scherzinger teaches a method for amplifying a DNA molecule comprising amplifying a template DNA molecule under isothermal conditions in a reaction mixture that comprises the DNA template, wild-type T7 DNA polymerase, a helicase from bacteriophage T7, a primase from bacteriophage T7, and a single-stranded DNA binding protein (see page 546, column 1). The amplification method of Scherzinger does not require the

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addition of exogenously added primers, and the template DNA molecule does not have a terminal protein covalently attached to either 5' end. Scherzinger teaches that the amount of amplified product produced by the method is as much as 4-fold greater than the amount of template put into the reaction mixture (page 549, column 2).

Regarding claims 124-127, 157, and 158, Scherzinger does not teach 100-10,000,000-fold amplification.

Regarding claims 128, 159, 166, and 168, Scherzinger does not teach exponential amplification.

Walker teaches an isothermal exponential DNA amplification method. The method of Walker utilizes a nicking enzyme to repeatedly generate substrates for a strand displacing DNA polymerase, and thereby, permit isothermal amplification (see abstract, pages 1691-1693, and Figures 1-2). Regarding claims 124-127, 157, and 158, Walker teaches that the method permits  $10^7$ -fold amplification (see abstract and Table 1). Regarding claims 128, 159, 166, and 168, since the nicking enzyme nicks both strands of the double-stranded nucleic acid template, the method permits exponential amplification by the strand displacing DNA polymerase (see Fig. 2).

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to apply the teachings of Walker to the method resulting from the combined teachings of Scherzinger, Sorge, and Tabor. An ordinary artisan would have been motivated to include a nicking enzyme in the reaction mixture of Scherzinger, since Walker taught that the use of an enzyme that nicked both strands of a double-stranded nucleic acid was useful for separating these double-stranded products of nucleic acid amplification reactions, thereby permitting exponential and isothermal amplification. An ordinary artisan would have recognized that inclusion of a

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nicking enzyme in the reaction mixture of Scherzinger would have improved the method by permitting exponential rather than linear amplification. An ordinary artisan would have had a reasonable expectation of success in using a nicking enzyme in the reaction mixture of Scherzinger, since nicking enzymes were well known in the art, and Tabor taught that the 3' to 5' exonuclease-deficient T7 DNA polymerase was capable of initiating strand-displacement synthesis at nicks (page 6447, column 2). Thus, the methods of claims 124-128, 157-159, 166, and 168 are *prima facie* obvious in view of the combined teachings of Scherzinger, Sorge, Tabor, and Walker.

6. Claim 140 is rejected under 35 U.S.C. 103(a) as being unpatentable over Scherzinger et al. (European Journal of Biochemistry (1977) 72: 543-558; cited previously) in view of Sorge et al. (US 5,556,772; cited previously) and further in view of Tabor et al. (The Journal of Biological Chemistry (1989) 264(11): 6447-6458; cited previously) and further in view of Bernstein et al. (Proceedings of the National Academy of Sciences, USA (1988) 85: 396-400; cited previously).

The combined teachings of Scherzinger, Sorge, and Tabor result in the method of claims 1, 11, 129-139, 141-147, 156, and 165, as discussed above.

Scherzinger teaches using the 66-kDa or 58-kDa form of the T7 gene 4 protein rather than the 63-kDa form required by claim 140.

Bernstein compared the 56 kDa and 63 kDa forms of the T7 gene 4 protein (see abstract). Regarding claim 140, Bernstein teaches that the 7 kDa region absent from the 56 kDa form of the gene 4 protein is required for primase activity (see abstract and page 398).

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It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to apply the teachings of Bernstein to the method resulting from the combined teachings of Scherzinger, Sorge, and Tabor. An ordinary artisan would have been motivated to utilize the 63-kDa form of the T7 gene 4 protein in the reaction mixture taught by Scherzinger, since Bernstein taught that this protein contained the 7 kDa region critical for primase activity (see abstract and page 398). An ordinary artisan would have had a reasonable expectation of success in doing so, since Bernstein taught a method for purifying this protein (page 396, column 1). Thus, the method of claim 140 is *prima facie* obvious in view of the combined teachings of Scherzinger, Sorge, Tabor, and Bernstein.

7. Claims 148 and 149 are rejected under 35 U.S.C. 103(a) as being unpatentable over Scherzinger et al. (European Journal of Biochemistry (1977) 72: 543-558; cited previously) in view of Sorge et al. (US 5,556,772; cited previously) and further in view of Tabor et al. (The Journal of Biological Chemistry (1989) 264(11): 6447-6458; cited previously) and further in view of Dickinson et al. (Journal of Cell Science (1983) 60: 355-365; cited previously).

The combined teachings of Scherzinger, Sorge, and Tabor result in the method of claims 1, 11, 129-139, 141-147, 156, and 165, as discussed above.

These references do not teach including a nucleotide diphosphokinase in the amplification reaction.

Dickinson teaches the nucleotide diphosphokinase is required for DNA replication in yeast (see summary on page 355).

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It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to include a nucleotide diphosphokinase in the reaction mixture of Scherzinger. Since Dickinson taught that this enzyme was required for DNA replication, an ordinary artisan would have been motivated to further include this enzyme in the reaction mixture of Scherzinger in order to improve the ability of the *in vitro* system to synthesize DNA. Since purified forms of this enzyme were commercially available at the time of invention, an ordinary artisan would have had a reasonable expectation of success in incorporating this essential enzyme into the reaction mixture of Scherzinger. Thus, the methods of claims 148 and 149 are *prima facie* obvious in view of the combined teachings of Scherzinger, Sorge, Tabor, and Dickinson.

8. Claims 148 and 150 are rejected under 35 U.S.C. 103(a) as being unpatentable over Scherzinger et al. (European Journal of Biochemistry (1977) 72: 543-558; cited previously) in view of Sorge et al. (US 5,556,772; cited previously) and further in view of Tabor et al. (The Journal of Biological Chemistry (1989) 264(11): 6447-6458; cited previously) and further in view of Peller (Biochemistry (1977) 16(3): 387-395; cited previously).

The combined teachings of Scherzinger, Sorge, and Tabor result in the method of claims 1, 11, 129-139, 141-147, 156, and 165, as discussed above.

These references do not teach including an inorganic pyrophosphatase in the amplification reaction.

Peller investigated the role of pyrophosphate hydrolysis during *in vitro* synthesis of bacteriophage T7 DNA (see abstract). Peller sought to develop a thermodynamic explanation for the observation that nucleic acids generated by cell-free *in vitro* synthesis systems often

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produced products at the small end of the size spectrum (page 387, column 1). Peller stated, “The achievement of both very high molecular weights and sharply peaked size distributions in polynucleotides synthesized *in vitro* will require coupling to inorganic pyrophosphatase action as *in vivo* (see abstract).”

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to include an inorganic pyrophosphatase in the isothermal amplification reaction mixture taught by Scherzinger. As noted above, Peller expressly taught that synthesis of nucleic acids of high molecular weight required inorganic pyrophosphatase activity (see abstract). An ordinary artisan would have been motivated by these teachings of Peller to further include this enzyme in the reaction mixture of Scherzinger in order to improve the ability of the *in vitro* system to synthesize high molecular weight DNA. Since purified forms of this enzyme were commercially available at the time of invention, an ordinary artisan would have had a reasonable expectation of success in incorporating this essential enzyme into the reaction mixture of Scherzinger. Thus, the method of claims 148 and 150 are *prima facie* obvious in view of the combined teachings of Scherzinger, Sorge, Tabor, and Peller.

9. Claims 148, 151 and 152 are rejected under 35 U.S.C. 103(a) as being unpatentable over Scherzinger et al. (European Journal of Biochemistry (1977) 72: 543-558; cited previously) in view of Sorge et al. (US 5,556,772; cited previously) and further in view of Tabor et al. (The Journal of Biological Chemistry (1989) 264(11): 6447-6458; cited previously) and further in view of Nakai et al. (The Journal of Biological Chemistry (1993) 268(32): 23997-24004; cited previously).



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The combined teachings of Scherzinger, Sorge, and Tabor result in the method of claims 1, 11, 129-139, 141-147, 156, and 165, as discussed above.

These references do not teach including an ATP regeneration system comprising creatine kinase and phosphocreatine in the amplification reaction.

Nakai teaches methods of conducting *in vitro* DNA synthesis reactions using the T7 replication system (page 23998, column 1). Regarding claims 148, 151, and 152, Nakai teaches that the reaction mixture includes an ATP regenerating system that includes phosphocreatine and creatine kinase (page 23998, column 1).

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to include an ATP regeneration system comprising creatine kinase and phosphocreatine in the isothermal amplification reaction mixture taught by Scherzinger. As noted above, Nakai taught conducting *in vitro* DNA synthesis reactions using the T7 replication system in the presence of an ATP regeneration system comprising creatine kinase and phosphocreatine (page 23998, column 1). An ordinary artisan would have been motivated by these teachings of Nakai to further include the ATP regeneration system in the reaction mixture of Scherzinger in order to improve the ability of the *in vitro* system to synthesize DNA. Since creatine kinase and phosphocreatine were commercially available at the time of invention, an ordinary artisan would have had a reasonable expectation of success in incorporating an ATP regeneration system into the reaction mixture of Scherzinger. Thus, the method of claims 148, 151, and 152 are *prima facie* obvious in view of the combined teachings of Scherzinger, Sorge, Tabor, and Nakai.

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10. Claims 153 and 154 are rejected under 35 U.S.C. 103(a) as being unpatentable over Scherzinger et al. (European Journal of Biochemistry (1977) 72: 543-558; cited previously) in view of Sorge et al. (US 5,556,772; cited previously) and further in view of Tabor et al. (The Journal of Biological Chemistry (1989) 264(11): 6447-6458; cited previously) and further in view of Engler et al. (The Journal of Biological Chemistry (1983) 258(18): 11197-11205; cited previously).

The combined teachings of Scherzinger, Sorge, and Tabor result in the method of claims 1, 11, 129-139, 141-147, 156, and 165, as discussed above.

These references do not teach including T7 DNA ligase in the amplification reaction.

Engler teaches a method for conducting lagging strand synthesis using an *in vitro* T7 replication system (see abstract). Engler teaches that T7 DNA ligase activity is required for successful lagging strand synthesis (see abstract). Engler stated, "All steps in the replication of a lagging strand have been coupled in a model system that catalyzes the formation of covalently closed, circular, double-stranded DNA molecules using single-stranded viral DNA as template. A combination of four bacteriophage proteins, gene 4 protein, Form II of T7 DNA polymerase, gene 6 exonuclease, and DNA ligase, can accomplish this overall reaction (abstract)."

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to include T7 DNA ligase in the isothermal amplification reaction mixture of Scherzinger. As noted above, Engler expressly taught that DNA ligase was required for lagging strand synthesis during *in vitro* replication (see above). An ordinary artisan would have been motivated by these teachings of Engler to include T7 DNA ligase in the reaction mixture of Scherzinger in order to obtain the ability to generate closed circular double-stranded DNA

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molecules from the closed circular single-stranded DNA template used by Scherzinger. Since Engler taught a method for purifying T7 DNA ligase (page 11198, column 2), an ordinary artisan would have had a reasonable expectation of success in adding this enzyme to the reaction mixture taught by Scherzinger. Thus, the methods of claims 153 and 154 are *prima facie* obvious in view of the combined teachings of Scherzinger, Sorge, Tabor, and Engler.

11. Claim 155 is rejected under 35 U.S.C. 103(a) as being unpatentable over Scherzinger et al. (European Journal of Biochemistry (1977) 72: 543-558; cited previously) in view of Sorge et al. (US 5,556,772; cited previously) and further in view of Tabor et al. (The Journal of Biological Chemistry (1989) 264(11): 6447-6458; cited previously) and further in view of in view of Jarvis et al. (The Journal of Biological Chemistry (1990) 265(25): 15160-15167; cited previously).

The combined teachings of Scherzinger, Sorge, and Tabor result in the method of claims 1, 11, 129-139, 141-147, 156, and 165, as discussed above.

These references do not teach that the reaction mixture further includes an additive selected from the group consisting of dextran, potassium glutamate, and DMSO.

Jarvis studied the effect of including high molecular weight polymers such as dextran or polyethylene glycol (PEG) on the stability and processivity of the T4 DNA replication complex (abstract and page 15161). Jarvis reported that PEG and dextran stabilized the DNA replication complex, and thereby, indirectly increased processivity of the polymerase (see Table 1 on page 15162). Jarvis stated, "Although the processivity of the polymerase alone is not directly effected by the addition of such polymers to the solution, macromolecular crowding does significantly stabilize the holoenzyme and thus indirectly increases the observed processivity of the

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holoenzyme complex (abstract).” Jarvis further stated, “These results suggest that the volume-occupied solution conditions prevalent in vivo can significantly stabilize holoenzyme DNA replication complexes, and thus support high rates and high apparent processivities of DNA synthesis (page 15166).”

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to include dextran in the isothermal amplification reaction mixture taught by Scherzinger. As noted above, Jarvis expressly taught that dextran stabilized the T4 DNA replication complex, and thereby, increased processivity of the polymerase. An ordinary artisan would have been motivated by these teachings of Jarvis to include dextran in the reaction mixture taught by Scherzinger in order to stabilize the T7 DNA replication complex, and thereby, improve polymerase processivity with the ultimate result being increased amplification efficiency and yield. An ordinary artisan would have expected a reasonable level of success in doing so, since the Jarvis observed increased processivity in the highly similar T4 replication system and further taught that that the crowding effect responsible for the observed stabilization/increased processivity was generally applicable (pages 15161 and 15166). Thus, the method of claim 155 is *prima facie* obvious in view of the combined teachings of Scherzinger, Sorge, Tabor, and Jarvis.

12. Claims 161-164 and 169 are rejected under 35 U.S.C. 103(a) as being unpatentable over Scherzinger et al. (European Journal of Biochemistry (1977) 72: 543-558; cited previously) in view of Sorge et al. (US 5,556,772; cited previously) and further in view of Bernstein et al. (Proceedings of the National Academy of Sciences, USA (1988) 85: 396-400; cited previously)

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and further in view of Walker et al. (Nucleic Acids Research (1992) 20(7): 1691-1696; cited previously) and further in view of Tabor et al. (The Journal of Biological Chemistry (1989) 264(11): 6447-6458; cited previously).

The combined teachings of Scherzinger, Sorge, and Bernstein result in the method of claim 24, as discussed above.

Regarding claim 169, Scherzinger teaches a method for amplifying a DNA molecule comprising amplifying a template DNA molecule under isothermal conditions in a reaction mixture that comprises the DNA template, wild-type T7 DNA polymerase, a helicase from bacteriophage T7, a primase from bacteriophage T7, and a single-stranded DNA binding protein (see page 546, column 1). The amplification method of Scherzinger does not require the addition of exogenously added primers, and the template DNA molecule does not have a terminal protein covalently attached to either 5' end. Scherzinger teaches that the amount of amplified product produced by the method is as much as 4-fold greater than the amount of template put into the reaction mixture (page 549, column 2).

Scherzinger does not teach 100-10,000,000-fold amplification as required by claims 161-163. Scherzinger also does not teach that the reaction further comprises a variant T7 DNA polymerase modified to possess reduced 3' to 5' exonuclease activity as required by claim 169. Scherzinger teaches using the 66-kDa or 58-kDa form of the T7 gene 4 protein rather than the 63-kDa form required by claim 169. Finally, Scherzinger does not teach exponential amplification as required by claims 164 and 169.

Sorge teaches a composition which comprises a DNA polymerase with substantial 3'-5' exonuclease activity and DNA polymerase modified to have reduced 3' to 5' exonuclease

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activity (column 2, lines 63-66). Sorge further teaches that wild-type T7 DNA possesses substantial 3' to 5' exonuclease activity (column 3, lines 44-47), whereas modified T7 DNA polymerase has reduced 3' to 5' exonuclease activity (column 4, lines 5-10). Regarding claim 169, Sorge teaches that conducting amplification reactions in the presence of a DNA polymerase that possesses substantial 3' to 5' exonuclease activity and a DNA polymerase substantially lacking in 3' to 5' exonuclease activity, "increases synthesis product yield, increased transcription product length, and the synthesis of polynucleotides that can not be synthesized by a given polymerase alone (column 3, lines 22-27)."

Bernstein compared the 56 kDa and 63 kDa forms of the T7 gene 4 protein (see abstract). Regarding claim 169, Bernstein teaches that the 7 kDa region absent from the 56 kDa form of the gene 4 protein is required for primase activity (see abstract and page 398).

Walker teaches an isothermal exponential DNA amplification method. The method of Walker utilizes a nicking enzyme to repeatedly generate substrates for a strand displacing DNA polymerase, and thereby permit isothermal amplification (see abstract, pages 1691-1693, and Figures 1-2). Regarding claims 161-163, Walker teaches that the method permits  $10^7$ -fold amplification (see abstract and Table 1). Regarding claims 164 and 169, since the nicking enzyme nicks both strands of the double-stranded nucleic acid template, the method permits exponential amplification by the strand displacing polymerase (see Figure 2).

Tabor teaches wild-type and variant forms of T7 DNA polymerase (see abstract). Regarding claims 161-164 and 169, Tabor teaches that the modified T7 DNA polymerase that lacks 3' to 5' exonuclease activity is capable of initiating strand-displacement synthesis at nicks (page 6447, column 2).

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It would have been *prima facie* obvious to one of ordinary skill in the art at the time of invention to apply the teachings of Sorge, Bernstein, and Walker to the method taught by Scherzinger. An ordinary artisan would have been motivated to further include a T7 DNA polymerase substantially lacking in 3' to 5' exonuclease activity in the reaction mixture taught by Scherzinger, since Sorge stated that amplification in the presence of a DNA polymerase that possesses substantial 3' to 5' exonuclease activity and a DNA polymerase substantially lacking in 3' to 5' exonuclease activity, "increases synthesis product yield, increased transcription product length, and the synthesis of polynucleotides that can not be synthesized by a given polymerase alone (column 3, lines 22-27)." An ordinary artisan also would have been motivated to utilize the 63-kDa form of the T7 gene 4 protein in the method taught by Scherzinger, since Bernstein taught that this protein contained the 7 kDa region critical for primase activity (see abstract and page 398). Finally, an ordinary artisan would have been motivated to include a nicking enzyme in the reaction mixture of Scherzinger, since Walker taught that the use of an enzyme that nicked both strands of a double-stranded nucleic acid was useful for separating these double-stranded products of nucleic acid amplification reactions, thereby permitting exponential and isothermal amplification. An ordinary artisan would have recognized that inclusion of a nicking enzyme in the reaction mixture of Scherzinger would have improved the method by permitting exponential rather than linear amplification. An ordinary artisan would have had a reasonable expectation of success in using a nicking enzyme in the reaction mixture of Scherzinger, since nicking enzymes were well known in the art, and Tabor taught that the 3' to 5' exonuclease-deficient T7 DNA polymerase was capable of initiating strand-displacement synthesis at nicks (page 6447, column

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2). Thus, the methods of claims 161-164 and 169 are *prima facie* obvious in view of the combined teachings of Scherzinger, Sorge, Bernstein, Tabor, and Walker.

***Response to Amendment***

13. The declaration under 37 CFR 1.132 filed on March 2, 2009 is insufficient to overcome the above rejections of claims 1, 11, 24, 124-159, 161-166, 168, and 169 under 35 U.S.C. 103(a) as set forth in the last Office action, because the declaration fails to set forth facts concerning why the observed results are considered to be unexpected. The evidence presented in the declaration is also not commensurate in scope with the claimed invention.

Point 5 of the declaration alleges that the claimed levels of amplification were unexpected and cites pages 5-8 and Examples 1, 2, & 4 of the specification to support this conclusion. Pages 5-8 of the specification simply allege that the yield obtained using the claimed methods is unexpectedly high, but provides neither evidence to support this conclusion nor a discussion of why the observed amplification yields should be considered to be unexpected compared to the closest prior art. Working Example 1 teaches conducting isothermal amplification and obtaining a reaction yield of 150,000 fold (see pages 21-24). Working Example 2 teaches improving the amplification yield to 1,500,000 fold by modifying the reaction conditions and including additional reagents (see pages 24-26). Example 4 describes methods of monitoring the progress of the amplification reaction in real-time (see pages 27-28) and does not appear to discuss amplification reaction yields. The working examples also do not provide any reasoning as to why the observed yields should be considered to be unexpected compared to the closest prior art.



As noted in MPEP 716.02(a), citing *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986), "Any differences between the claimed invention and the prior art may be expected to result in some differences in properties. The issue is whether the properties differ to such an extent that the difference is really unexpected." Also, as noted in MPEP 716.02(b), citing *Ex parte Gelles*, 22 USPQ2d 1318, 1319 (Bd. Pat. App. & Inter. 1992), "The evidence relied upon should establish 'that the differences in results are in fact unexpected and unobvious and of both statistical and practical significance.'" Furthermore, as noted in MPEP 716.02(b), citing *Ex parte Ishizaka*, 24 USPQ2d 1621, 1624 (Bd. Pat. App. & Inter. 1992, "[A]ppellants have the burden of explaining the data in any declaration they proffer as evidence of non-obviousness."

In this case, as discussed above, neither the declaration nor the passages of the specification cited in the declaration provide a discussion of why the observed amplification yields should be considered to be unexpected compared to the closest prior art. In the absence of such a discussion, it would appear that combining the teachings of the cited references and conducting routine optimization would necessarily result in the claimed amplification yields, since the combined teachings of the cited references suggest conducting isothermal amplification using the claimed reaction compositions. As noted in MPEP 716.02(c) citing *In re Gershon*, 372 F.2d 535, 538, 152 USPQ 602, 604 (CCPA 1967), "Expected beneficial results are evidence of obviousness of a claimed invention, just as unexpected results are evidence of unobviousness thereof." As discussed above, the teachings of Sorge, Bernstein, and Walker would have suggested to the ordinary artisan that using the claimed reaction mixtures and conducting exponential amplification would result in the benefit of increasing the reaction yield. Therefore,

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in the absence of a discussion of why the observed results should be considered unexpected compared to the closest prior art, the observed results would appear to be expected based on the teachings of the cited references.

It is also noted that the results presented in working examples 1 and 2 are not commensurate in scope with the claimed invention. As noted in MPEP 716.02(d) citing *In re Clemens*, 622 F.2d 1029, 1036, 206 USPQ 289, 296 (CCPA 1980), "Whether the unexpected results are the result of unexpectedly improved results or a property not taught by the prior art, the 'objective evidence of nonobviousness must be commensurate in scope with the claims which the evidence is offered to support.'"

In this case, the claimed methods are much broader in scope compared to the methods described in Examples 1 and 2. The methods described in the working examples recite specific reagent concentrations and combinations of enzymes and reagents that are never recited in the claims as a single embodiment. For example, in working example 2, the isothermal amplification reaction is conducted using a reaction mixture comprising the  $\Delta 28$  T7 DNA polymerase, native T7 DNA polymerase, 63-kDa gene 4 protein, *E. coli* single-stranded DNA binding protein, and at least some of the following six enzymes: creatine kinase, nucleoside diphosphokinase, inorganic pyrophosphatase, T7 single-stranded DNA binding protein, T7 gene 6 exonuclease, and T7 DNA ligase (see pages 24-26). All of the reaction mixtures recited in the pending claims are broader, containing fewer components and with no concentration or buffer requirements. As a result, it is not clear that the observed amplification yields would necessarily extend to the broader embodiments recited in the claims. Also, some of the claimed methods encompass amplification yields (*e.g.* at least 10-fold, at least 100-fold) that are much lower than

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those obtained in Examples 1 and 2, and there is no evidence to suggest that obtaining a moderate increase in the yield (*e.g.* 10-fold) would be unexpected compared to the closest prior art.

In point 7 of the declaration, Applicant states that modification of the method of Scherzinger to achieve the claimed amplification yields would have required more than routine optimization. In point 8, Applicant states that the method of Sorge requires the use of exogenous primers, and therefore, is very different from the method described by Scherzinger, which is conducted in the absence of exogenous primers. Point 8 of the declaration further states that there are no teachings in the Sorge reference that would have led the ordinary artisan to apply the teachings therein to the method of Scherzinger. Point 9 of the declaration states that the Tabor reference is directed to site-directed mutagenesis, and therefore, the reference does not provide the ordinary artisan with a reasonable expectation of success in obtaining the claimed amplification yields.

These arguments were not persuasive, because they constitute Applicant's opinion and are not supported by factual evidence. As discussed above, the teachings of the cited references suggest that the observed results are not unexpected.

In view of the foregoing, when all of the evidence is considered, the totality of the rebuttal evidence of nonobviousness fails to outweigh the evidence of obviousness. Accordingly, the rejections have been maintained.

***Response to Arguments***

14. Applicant's arguments filed on March 2, 2009 have been fully considered, but they were not persuasive.

Regarding the rejection of claims 1, 11, 129-139, 141-147, 156, and 165 under 35 U.S.C. 103(a) as being unpatentable over Scherzinger in view of Sorge and further in view of Tabor and the rejection of claim 24 under 35 U.S.C. 103(a) as being unpatentable over Scherzinger in view of Sorge and further in view of Bernstein, Applicant first argues that there is no motivation to apply the teachings of Sorge to the method of Scherzinger since these references pertain to amplification methods conducted using exogenous primers, whereas the method of Scherzinger pertains to an amplification method conducted in the absence of exogenous primers (see pages 10-13).

In response to this argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

In this case, as discussed above, an ordinary artisan would have recognized that the teachings of Sorge regarding the benefits of using a mixture of DNA polymerases when conducting an amplification reaction (*i.e.* increased product yield, increased product length, and the synthesis of polynucleotides that can not be synthesized by a given polymerase alone – see

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column 3, lines 22-27) would be relevant to any polymerase-mediated amplification process, such as the isothermal amplification method of Scherzinger. Therefore, an ordinary artisan would have been motivated to apply the teachings of Sorge to the method of Scherzinger. An ordinary artisan would have had a reasonable expectation of success in doing so, since Scherzinger utilized T7 DNA polymerase in the isothermal amplification method (see page 549). An ordinary artisan also would have had a reasonable expectation of success in obtaining amplification reaction yields of at least 10-fold via routine optimization of the reaction conditions, since Sorge taught that the use of the disclosed mixture polymerase was associated with increased reaction yield (column 3, lines 22-27).

Applicant also argues that the Tabor reference does not remedy the deficiencies in the Scherzinger and Sorge references, since the reference only describes wild type and variant forms of T7 DNA polymerase (see page 12). This argument was not persuasive, because the Tabor reference is only relied upon for its teachings regarding the inherent properties of the T7 DNA polymerases disclosed by Sorge and Scherzinger.

Applicant also argues that the Tabor declaration filed under 37 CFR 1.132 is sufficient to overcome the rejection (see pages 12-13). This argument was not persuasive, because as discussed in greater detail above, the declaration was ineffective to overcome the rejections under 35 U.S.C. 103(a).

Since Applicant's arguments were not persuasive, the rejections have been maintained.

Regarding the rejections of claims 124-128, 157-159, 161-164, 166, 168, and 169 made under 35 U.S.C. 103(a), Applicant first argues that the teachings of Walker do not remedy the deficiencies in the primary combinations of references (see pages 15 and 19). This argument

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was not persuasive, because as discussed above, the primary combinations of references suggest all of the limitations of the independent claims. The Walker reference is only relied upon for its teachings cited above regarding the benefits of conducting isothermal exponential amplification methods in an exponential fashion.

Applicant also argues that there is no motivation to apply the teachings of Walker regarding primer-based amplification methods to the primer-free system of Scherzinger and that the ordinary artisan would not have had a reasonable expectation of success in obtaining the claimed amplification yields based on the teachings in the cited references (see pages 15-16 and 19). Applicant also cites the Tabor declaration to support this argument (see page 15).

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

In this case, as discussed above, an ordinary artisan would have been motivated to apply the teachings of Walker to the method resulting from the combined teachings of Scherzinger, Sorge, and Tabor or the method resulting from the combined teachings of Scherzinger, Sorge, and Bernstein in order to obtain the ability to conduct the isothermal amplification method in an exponential manner, and thereby, further increase the product yield. Since exponential amplification methods, such as the method disclosed by Walker, were inherently capable of

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achieving amplification yields of several million fold, the ordinary artisan would have had a reasonable expectation of success in obtaining the claimed amplification yields upon application of the teachings of Walker in combination with routine optimization to yield an isothermal exponential amplification method. It is also noted that the Applicant's arguments regarding the Tabor declaration were not persuasive, because as discussed in greater detail above, the declaration was ineffective to overcome the rejections made under 35 U.S.C. 103(a). Since Applicant's arguments were not persuasive, the rejections have been maintained.

Regarding the rejections of claims 140 and 148-155 made under 35 U.S.C. 103(a), Applicant argues that the primary combination of references (Scherzinger, Sorge, & Tabor) does not render obvious the methods of independent claim 1, and that the additional secondary references do not overcome this deficiency (see pages 16-18). This argument was not persuasive, because as discussed above, the combined teachings of Scherzinger, Sorge, and Tabor render obvious the method of claim 1. Since Applicant's arguments were not persuasive, the rejections have been maintained.

### ***Conclusion***

15. No claims are currently allowable.

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

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the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANGELA BERTAGNA whose telephone number is (571)272-8291. The examiner can normally be reached on M-F, 9- 5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Amb

/GARY BENZION/

Supervisory Patent Examiner, Art Unit 1637